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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/086,072	02/27/2002	Laurie DeLeve	13761-7065	1401

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EXAMINER	
SHARAREH, SHAHNAM J	

ART UNIT	PAPER NUMBER
1617	

DATE MAILED: 08/26/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/086,072	DELEVE, LAURIE	
	Examiner	Art Unit	
	Shahnam Sharareh	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 June 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-17 and 20* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *16 and 17* is/are allowed.

6)☒ Claim(s) *1-5,7,9-12,14 and 20* is/are rejected.

7)☒ Claim(s) *6,8,13 and 15* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *6/10/2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Amendment filed on June 10, 2005 has been entered. Claims 1-17, 20 are pending.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

1. Claim 20 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The language of "supporting liver function" renders the claim vague. It is not clear how the liver function is being supported and what the metes and bounds of the claim in fact is?

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 1-5, 7, 9, 10-11,14 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for administration of doxycycline or propionic acid derivatives for treating sinusoidal obstruction syndrome at a specific dose, it does not reasonably provide enablement for methods of treating such condition with all compounds that can potentially inhibit matrix metalloproteinases at any given dose. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to ascertain the entire scope of the

term "matrix metalloproteinase inhibitor" and thus practice the invention commensurate in scope with these claims.

In particular, the specifications fail to enable the skilled artisan to practice the invention without undue experimentation. As held *in ex parte Forman* (230 USPQ 546, BdPatApp & Int.) and *In re Wands* (858 F.2d 731, 8 USPQ2d 1400, 1404, Fed. Cir. 1988) several factors are considered when determining if the specification of an application allows the skilled artisan to practice the invention without undue experimentation. In the instant case, the claims appear to be directed toward using such compounds that are not enabled by describing a function and thus reaching through a nonenabled invention. However, as set forth below, specification fails to enable one of ordinary skill in the art to practice the full scope of the claims.

Due to the unpredictable nature of the art, the level of one of ordinary skill in the art in assessing the entire scope of the term "matrix metalloproteinase inhibitor," the lack of working example and adequate guidance as to how to prepare all such compounds falling within the such language the specification fails to enable one of ordinary skill in the art to practice the claimed scope of the invention without undue experimentation.

(1) The nature of the invention:
The invention encompasses the entire genus of compounds that can inhibit the activity of metalloproteinase at any given dose.

(2) The state of the prior art
The state of art towards accomplishing such activity is directed to various tetracycline derivatives and propionic acid derivatives. The art does not provide a common unifying structure or a structural activity relationship that can classify compounds as matrix metalloproteinase inhibitors. Nor does the state of art clarify the dosing ranges of such compounds for treating sinosidal obstruction syndrome.

(3) The relative skill of those in the art

The relative skill of those in the art is high and encompasses medicinal chemists and clinical pharmacologists.

(4) The predictability or unpredictability of the art

The unpredictability of the chemical art is very high as to determination of all compounds that can provide effective matrix metalloproeinase inhibition at the level of MMP or MMP-2 isoenzymes. Specifically, the state of art is unpredictable as to the dosing ranges of such compounds that can provide adequate inhibition of upregulation of MMP-9 or MMP-2 isoenzymes for treating sinusoidal obstruction syndrome or chemotherapy induced liver disease.

(5) The breadth of the claims

The claims are very broad. The instant claims are directed to the use of compounds that are identified by their ability to perform the function of inhibiting a matrix metalloproteinase and that can inhibit up-regulation of MMP-9 and/or MMP-2 isoenzymes. Accordingly, the claims appear to be directed to the use of a class of compounds that are identified by a function. The use of a functional limitation at the point of novelty is well explained by the Courts. Attention is directed to *General Electric Company v. Wabash Appliance Corporation et al* 37 USPQ 466 (US 1938), at 469, speaking to functional language at the point of novelty as herein employed: "the vice of a functional claim exists not only when a claims is "wholly" functional, if that is ever true, but when the inventor is painstaking when he recites what has already been seen, and then uses conveniently functional language at the exact point of novelty." Furthermore, the Court reasons that such language does not adequately "inform the public during the life of the patent of the limits of the monopoly asserted." *General Electric Company v. Wabash Appliance Corporation et* supra, at 468. Functional language at the point of novelty, as herein employed by Applicants, is further admonished in *University of California v. Eli Lilly and Co.* 43 USPQ2d 1398 (CAFC 1997) at 1406: stating this usage does "little more than outlin[e] goals appellants hope the recited invention achieves and the problems the invention will hopefully ameliorate." Also see *University of Rochester v. GD Searle & Co., Inc.* W.D.N.Y. 2003, (U.S. District Court for Western District United of New York).

Here, applicant's claims are directed to the use of a class of compounds that can be identified by a functional limitation. Applicants functional language at the point of novelty fails to meet the requirements set forth under 35 USC 112, first paragraph, because it is merely no more than an outline goal that the claimed method attempts to achieve without informing the public the limits of the monopoly asserted. Simply stated, the presented claims are an invitation to experiment, not reciting a specific compounds useful for practicing the instant invention.

(6) The amount of direction or guidance presented

The specification provides guidance to specific compounds known in the art to inhibit metalloproteinase. No commonality as to a common core or chemical characteristics has been described. Further, to the extent applicable to doxycycline, the claimed clinical end-point appears to be a function of specific and unexpected dosing requirements, and not a function of a novel or unobvious chemical moiety.

(7) The presence or absence of working examples

As stated above, the specification discloses specific set of compounds and not the entire genus of compounds encompassed by the term "matrix metalloproeinase inhibitor."

(8) The quantity of experimentation necessary

Since the ability of the compound to perform the described function is paramount to the scope of enablement of the claimed invention, the claims cannot be practiced of predicted by a prior knowledge. Rather, the scope of the claims must be determined on a case to case by painstaking experimental study. Accordingly, one of ordinary skill in the art would be burdened with undue experimentation study" to determine the all of the compounds and effective doses capable of being used in the instant methods.

Claim Rejections - 35 USC § 102

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

3. Claims 1-5, 9, 10-12, 20 are rejected under 35 U.S.C. 102(b) as being anticipated by Leitersdorf et al, Clinical Nephrology 1997, 48/1 (48-51).

The instant claims are directed to methods of prophylaxis or treating Sinusoidal Obstruction Syndrome in a human patient in need thereof comprising administering an effective amount of a matrix metalloproteinase inhibitor that inhibits up-regulation of MMP-9 and/or MMP-2 isoenzymes. Note that any degree of inhibition of MMP isoenzymes reads on the pending claims.

Leitersdorf teaches administration of tetracyclines such as doxycycline in amount of about 100-600 mg/day to patients who have undergone liver transplantation and have developed nocardiosis. Such patients are viewed to fall within the scope of the instantly

claimed patients in need because they are status post-liver transplantation and are subjected to immunosuppressive therapies that fall within the scope of the instantly claimed chemotherapy.

Note that in claims drawn to a process, the intended use must result in a manipulative difference as compared to the prior art. See *In re Casey*, 370 F.2d 576, 152 USPQ 235 (CCPA 1967) and *In re Otto*, 312 F.2d 937, 939, 136 USPQ 458, 459 (CCPA 1963). Since Leitersdorf method meets the administration step and the patient population of the instant claims, it would inherently achieve the purpose of the instantly claimed invention by prophylactically treating human patients that are at risk of developing sinusoidal obstruction syndrome or prophylactically treating patients at risk of chemotherapy induced liver disease including sinusoidal obstruction syndrome.

Since the instant claims are not directed to any dosing range, Examiner has taken the position that Leitersdorf's patients receiving doxycycline, the same compound instantly employed, at least upon receiving cumulative doses would inherently experience a degree of inhibition on the upregulation of MMP-9 or MMP-2 isoenzymes.

Response to Arguments

Applicant's arguments filed June 10, 2005 have been fully considered but they are not persuasive.

4. With respect to the rejection of claims under the 35 USC § 112, first paragraph, Applicant argues that matrix metalloproteinase inhibitor (MMP inhibitors) that inhibits up-regulation of MMP-9 and/or MMP-2 isoenzymes are defined in the art and well known at the time of this application was filed. Applicant then submits the copies of the article

authored by Whittaker et al (1999) Chem. Rev. 99:2735-2276 ("Whittaker"), and Tamara et al (1998). 41:640-649, ("Tamara"), Wada et al (2002), J.Med. Chem 45:219-232 ("Wada") to support that such compounds are well known.

In response Examiner states that the issue here is not whether a sample or a genus of compounds known as MMP inhibitors are described in the art. Rather, whether the instant specification has adequately met the standard under 35 USC 112, First Paragraph, and enabled the entire scope of the claims. Here, the claims are directed to the use of the entire genus of MMP inhibitors for treating Sinusoidal Obstruction Syndrome by inhibition of the up-regulation of MMP-9 or MMP-2 isoenzymes. The factual analysis of *Wands* Factors articulated above leads to the conclusion that the specification does not meet the requirement under 112 first paragraph in enabling the entire scope of the instant claims.

5. With respect to the anticipation rejection, Applicant argues that the instant claims are directed to higher doses of doxycycline and is beyond the doses disclosed in the cited art. In response, Examiner states that the rejected claims are not directed to any specific dosing, rather, they are directed to effective doses that inhibits a function of MMP. Since the compound of Lisesdorf is the same as instantly employed, Examiner has taken the position, that at least a degree of such inhibition is achieved, by cumulative doses of the same compound.

6. The Declaration under CFR 1.132 filed June 10, 2004 is insufficient to overcome the rejection of claims 1-5, 9, 10-12, 20 based upon Leitersdorf as set forth in the last Office action because it is directed to achieving the claimed clinical results with specific

dosing regimens and not the individual rejected claims. Thus, there is no showing that the objective evidence of nonobviousness is commensurate in scope with the claims. See MPEP § 716. In the Declaration, Applicant argues that even though not explicitliy stated, the DeLeve article published in the Journal of Gastroenterology 2003, infers that lower doses of doxycycline does not prevent clinical sign of SOS in the animals. Again, aside from the fact that such line of arguments are void of any substantive evidence, the arguments are not commensurate with the scope of the rejected claims. All that is required by the instant claims is to administer doxycycline in amounts that leads to the inhibition of the up-regulation of MMP-9 or MMP-2 isoenzymes. There is no evidence provided that at least the cumulative doses of doxycycline in the population of Leitersdorf causes at least some degree of MMP-2 or MMP-9 inhibition. Thus, Leitersdorf inherently meets the instantly claimed intended purpose.

Allowable Subject Matter

7. Claims 6, 8, 13, 15 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

8. Claims 16-17 are allowed.

Conclusion

9. No claims are allowed. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shahnam Sharareh whose telephone number is 571-272-0630. The examiner can normally be reached on 8:30 am - 6:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreenivasan Padmanabhan, PhD can be reached on 571-272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

SREENI PADMANABHAN
SUPERVISORY PATENT EXAMINER